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10/530,601	04/07/2005	Chantal Catharina Maria Appeldoorn	05-287	7172

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EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/530,601	APPELDOORN ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/7/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP03/11457 filed 10/13/2003 and claims priority to European filed application, EPO 02079232.1, filed 10/11/2002.

Claims 1-9 and 14-16 are currently pending and are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for p-selectin inhibitors with formula Ia, 2, 3, 6d, 6f, 6h and 6i and their use in a screening method and for the method for treating or inhibiting disease associated with p-selectin does not reasonably provide enablement for a compound of formula Ia or Ib wherein R4 or R5 represents any substituent comprising at least one carbon, or any R3 group or any R2 moiety bearing at least one negative charge. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to compounds of the general structure Ia and 1b and the method for using those compounds for a screening method and the

method for using said compounds for a condition associated with p-selectin. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

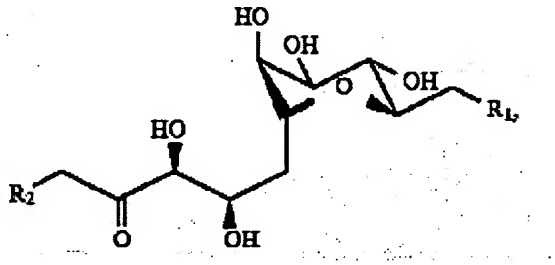
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The present invention relates to compounds of the general formula Ia, and in particular compounds 2, 3, 6d, 6f, and 6i which selectively bind to the adhesion molecule human P-selectin, to the use of such compounds for the preparation of pharmaceutical compositions for the treatment of P-selectin associated disorders, to conjugates, pharmaceutical carriers and drug delivery systems comprising said compounds, and to a method for determining whether a compound is capable of binding to P-selectin.

The state of the prior art:

Wong et. al. discloses that the use of compounds of the following structure and its isomers are well known for their ability to inhibit selectins, including P-selectin. (U.S. Patent No. 5,830,871, Column 2, lines 40 to Column 7; PTO-892, Cited by the examiner).



With one of the particular compound of the above formula, more than 80% inhibition of p-selectin was achieved. (Figure 6).

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The predictability or lack thereof in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the

statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation encompasses many, different, divergent functional substitutions at the R2-R5 positions giving various compounds with divergent and highly unpredictable properties. For example, the R4 group has an admittedly significant influence on the P-selectin binding activity. (Specification, Page 9, lines 10-15). However, R4 is defined in claim 1 as "any substituent comprising at least one carbon atom". In claim 1, R4 is defined as part of R1. i.e., R1 is QR4. (Figure 1). In case of tested compound 2, R1 is H. For compounds 6f and 6i, R4 is phenyl and naphthalene respectively. (Figure 1). For compounds 6i the R4 is (-CH2-CCl3). These three disclosed functional groups do not represent disclosure enabling one of ordinary skill in the art to practice the invention commensurate with the broad claims that include "any substitutent comprising at least one carbon atom." Similarly, the specification does not enable one of ordinary skill in the art to practice the invention commensurate with the breadth of the claims where R2-R5 are as claimed.

The breadth of the claims:

Claims 1-9 and 14-16 are very broad because they encompass compounds with wide varying functional groups in the R1-R5 positions including, peptides, nucleotides, inorganic coordinating groups and organic functional groups. These wide and diverse functional groups cover thousands of possible molecules and as such the claims are deemed very broad.

The amount of direction or guidance presented, and the presence or absence of working examples:

The specification contains guidance for the synthesis of compounds 2, 3, 6d, 6f, 6h and 6i. (Pages 15-17, examples 1 & 3). Furthermore, specification provides guidance to assay above said compounds for their activity against p-selectin. (Examples 2 & 4, Pages 15-17).

The specification does not provide guidance for the synthesis of compounds of formula Ia or Ib for a wide-ranging group of functionalities commensurate with the breadth of claims.

The quantity of experimentation necessary:

In order to determine which of the varying functions groups in the R2-R5 positions of the claimed compounds, one of ordinary skill in the art will have to perform substantial experimentation. Experimentation will include the synthesis of compound with many different functional groups in the R2-R5 positions and identifying varying functional groups for activity against p-selectin. Such experimentation will involve the commitment of highly skilled organic chemists, microbiologists, biochemists and those with expertise in combinatorial chemistry. As such, undue experimentation is necessary to practice the invention to its full scope.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And

"patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the ***Wands*** factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites "electron withdrawing moiety." The phrase is not clearly defined in the specification. Note that the description in terms of examples is not considered a concise definition. As such, said phrase renders the claim indefinite.

Claims 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations, " derivative", "conjugate" or "multimer" in the claim renders the claim herein indefinite. The recitations, " derivative", "conjugate" or

"multimer" of the compounds are not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to " derivative", "conjugate" or "multimer" of compounds herein. One of ordinary skill in the art would clearly recognize that derivatives and conjugates and multimers of the skeletal structural formula Ia would read on any those compounds having any widely varying groups that possibly substitute the compounds.

Any significant structural variation to a compound would be reasonably expected to alter its properties; e.g., physical, chemical, physiological effects and functions. Thus, it is unclear and indefinite as to the " derivative", "conjugate" or "multimer" of compounds herein encompassed thereby.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation "wherein R3 comprises an anchor moiety capable of anchoring the compound to a colloidal or microparticulate drug carrier" renders the claim indefinite. One of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to the compounds encompassed by said phrase herein.

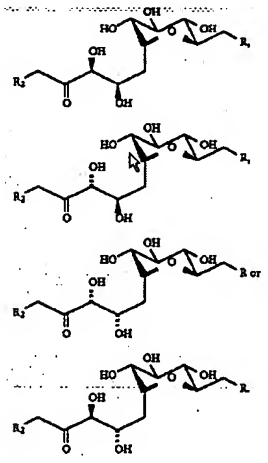
Claim Rejections - 35 USC § 103

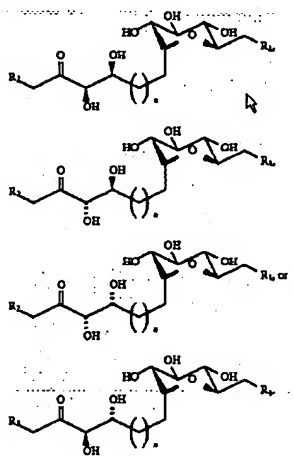
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-9 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et. al. (U.S. Patent No. 5,830,871; PTO-892, Cited by the examiner).

Wong et. al. discloses the use of compounds that have strong structural similarity with compounds of the generic formulae 1a and 1b of the instant application for the treatment of p-selectin. Wong et. al. discloses the following series of compounds. (Columns 5 and 7). Wong et. al. further discloses a method for determining whether a compound is capable of binding to selectin. (Column 13, lines 48-58).





Wong et. al. does not expressly disclose compounds with substituents "comprising at least one carbon" at the R4 position.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use compounds with "substituents with at least one carbon" at the R4 position because Wong et. al. broadly discloses compounds with strong structural similarity for the inhibition of P-Selectin.

One of ordinary skill in the art would have been motivated to use compounds with at least one carbon at the R4 position for the inhibition of p-selectin, because similar compounds are used for the inhibition of p-selectin. If the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species. It is a reasonable expectation that similar species usually have similar properties. See Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also, Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214. In fact, similar properties may formally be presumed when compounds are very close in structure. Dillon 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904, as noted in MPEP 2144.

Thus, claims 1-5, 8-9 and 14-16 are obvious over the combined teachings of the prior art.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et. al. (U.S. Patent No. 5,830,871; PTO-892, Cited by the examiner), in view of DeFrees et. al. (U.S. Patent No. 5,604,207; PTO-892, Cited by the

examiner), further in view of Wong et. al. (J.Am.Chem. Soc. 1997, 119, 8152-8158).

The disclosure of the '871 patent is disclosed above.

The '871 patent does not expressly disclose the use of phenyl or naphthyl substituent for analogue compounds of sialyl lewis x for the inhibition of p-selectin.

De Frees et. al. discloses the use of aryl, phenyl and naphthyl substituents on carbohydrate inhibitors or selectins. (Column 1, lines 15-20; and Scheme 2, Column 16, line 17 to Column 24). The inhibitory effect of compounds with phenyl and naphthyl substituents were significantly higher than that of those without said substituents. (Column 79-88, Table 4).

Wong et. al. discloses that selectin inhibitors with additional electrostatic and hydrophobic interactions have better binding ability. (Page 8153, Column 2, Paragraph 3, lines 3-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use compounds with aryl, phenyl and naphthyl substitents because Wong et. al. broadly discloses compounds with strong structural similarity for the inhibition of P-Selectin and DeFrees et. al. discloses that the use of aryl, phenyl and naphthyl substituents on carbohydrate inhibitors of selectins.

One of ordinary skill in the art would have been motivated to use compounds with aryl, phenyl and naphthyl substitents for the inhibition of p-selectin, because similar compounds are used by Wong et. al. ('871 patent) for the inhibition of p-selectin and DeFrees et. al. discloses the use of aryl, phenyl

and naphthyl substituents on carbohydrate inhibitors of selectins with increased effectiveness and Wong et. al. (JACS) teaches the increased effectiveness of selectin inhibitors with hydrophobic and electrostatic substituents.

Thus, claims 6 and 7 are obvious over the combined teachings of the prior art.

Conclusion: No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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